IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	
GUERIN-MARCHAND ET AL	Group Art Unit: 1645
Serial No.:09/837,344	Examiner: N. Minnifield
Filed: April 19, 2001	
For: PEPTIDE SEQUENCES SPECIFIC FOR THE HEPATIC STAGES OF P. FALCIPARUM BEARING EPITOPES CAPABLE OF STIMULATING THE T LYMPHOCYTES	

1.132 DECLARATION

Hon. Commissioner of Patents
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I, Pierre Druilhe do hereby declare the following:

(1) I am currently the director of the Biomedical Parasitology Unit at Institut Pasteur in Paris, France and have been the director of this department for many years. As can be seen from my attached *Curriculum Vitae*, I have published 260 articles and have 10 U.S. Patents issued in my name. I am one of the inventors of the above-captioned U.S. patent application.

(2) I have read the last U.S. Official Action dated February 10, 2005, for the above-identified patent application. It is my understanding that the Examiner deems that the claims directed to vaccines cannot be produced by a scientist using the disclosure of the above-captioned specification since the specification does not teach a scientist how to obtain a malaria vaccine. It appears that the Examiner's reasoning in maintaining this rejection is that the specification purportedly only describes the construction of a Genomic DNA Library and the

provides further immunological testing of the chosen clones, as well as conclusions reached by this testing. I respectfully disagree with the Examiner for the following reasons.

(3) The specification clearly describes immunological responses of subjects exposed to malaria. More specifically, the immunization of mice with the LSA-R-NR proteins and LSA-R peptides of mice of different haplotypes with peptides LSA-R, LSA-J and LSA-NR and responses of the lymphocytes of subjects exposed to malaria indicated that a T-epitope existed in the LSA-R peptide, as well as a B epitope. Other results with more than 500 individuals exposed to malaria should that this T epitope was recognized by the antibodies of about 95% of the subjects studied in Senegal, Leppervoln, Madagascar and Kenya. Responses of lymphocytes obtained from 5 adult African subjects exposed to malaria and more than 200 adult African subjects confirmed that a T epitope of the LSA molecule was defined by the amino acid contained in the synthetic sequence of the peptide LSA-NR.

(4) Lymphocytes of chimpanzees, which were immunized using the LSA-R-NR recombinant protein (SEQ ID NO:19) , confirmed that this protein contained a T epitope. In this regard, the chimpanzees were immunized at 15 day intervals and production of antibodies specific for LSA-R-NR was demonstrated. 60% of the lymphocytes were of the CD8+ phenotype, which corresponds to cytotoxic T lymphocytes.

(5) The specification also discloses studies on mice that were injected with the recombinant protein LSA-R-NR and proof of B epitopes in the LSA-R-NR protein. Further studies conducted in sera taken from 120 African subjects confirmed that the peptide LSA-NR has a B epitope and that this epitope was recognized by 65% of the subjects.

(6) The specification also discloses that chimpanzees were immunized with LSA-R-NR and then further injected with an intravenous injection of 28 million sporozoites of *P. falciparum.* Control chimpanzees in which no immunization occurred were also inoculated in the same manner. Liver biopsies of the immunized chimpanzees were taken on the 6^{th} day after infection. The biopsies of the immunized chimpanzees showed the existence of cellular reaction, lympho-monocytic, around

the hepatic schizonts, infiltrating the schizonts and capable of destroying them. Such images were not observed in the control group.

(7) The cytolytic capacity of the lymphocytes on the immunized chimpanzees in paragraph (6) was further analyzed using a chromium 51 label. The results illustrated that the T epitopes are capable of activating cytolytic T lymphocytes for the LSA-R-NR sequence.

(8) Thus, for the results obtained in the above paragraphs (3) to (7) the following was concluded about the LSA-R-Nr (536) polypeptide:

(a) that this polypeptide is recognized by antibodies originating from subjects with malaria;

(b) that this polypeptide is recognized by sera of chimpanzees immunized therewith;

(c) that this polypeptide induces the function of antibodies (B epitopes);

(d) that this polypeptide induces proliferative responses of T lymphocytes indicating the presence of T epitopes in both chimpanzees and man;

(e) that the polypeptides NR and TER include a major T epitope and a B epitope for man as well as for mouse and the chimpanzee.

(9) Further studies were undertaken with Aotus monkeys confirming the presence of these B and T epitopes and the good antigenicity, as demonstrated in Perlaza et al, Infection and Immunity July 1998 p. 3423-3428, previously of record. In fact this paper indicates that in various types of monkeys such as *Aotus*, *Saimiri* and *Cebus* monkeys liver schizogony can be obtained with *P. falciparum* strains without the need for previous adaptation to these monkeys. Thus, this animal model can be used for preclinical development of pre-erythrocytic malaria vaccines.

(10) Therefore, since the peptide LSA-R-NR (SEQ ID NO:19) contains both T and B epitopes, larger sequences such as those of SEQ ID Nos 39-42 and 43-46, which contain the LSA-R-NR sequence also contain both T and B epitopes.

(11) Thus, the present specification clearly demonstrates that several polypeptides obtained by the methods in the specification have T epitopes, B epitopes or both and thus induce a wide range of immune responses.

(12) It appears that the Examiner has taken a strict interpretation of the word "vaccine" since at page 6 of the Official Action, the Examiner states that "the definition of a vaccine is a product that provides protection (prophylaxis) against infection, in this case protection against malaria." However, it is well known that a vaccine can either block the effects of the pathogen toxins or prime the immune system against the pathogen such that infection is brought under control more quickly. The latter is done through the vaccine's capability to stimulate antibody (B cells) and T cell responses that can then respond quickly to infection and prevent the pathogen from causing clinical illness.

(13) Indeed, vaccination works by producing T cell and B cell responses. Thus, when vaccinated cytotoxic T cells are produced by the immune system which recognizes the diseased cells and helper T cells assist in activating killer T cells and stimulate B cells, thus producing a cell-mediated immune response. The B cells secrete antibodies which attack malaria, thus producing a humoral immune response.

(14) Thus, it can be concluded that by discovering polypeptides having T epitopes and B epitopes as set forth in the present specification, a skilled artisan can produce a vaccine composition based on the disclosure of the specification. Indeed, I come to this conclusion, since additional studies have been made with LSA-1 antigens in endemic areas since the filing of the present patent application which have linked the LSA-1 antigen with protective immunity. More particularly B-cell and T-cell epitopes in LSA-1 have been associated with protective immunity as stated in the attached Document 1.

I also declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

28 March 2005

Date

Pierre DRUILHE

CURRICULUM VITAE

CURRICULUM VITAE : Pierre L. DRUILHE

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- "Maître de conférence des Universités" at the Faculty of Medicine "Necker-Enfants Malades", University Paris V, René Descartes

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EDUCATION :

1972 - Medical Degree, Paris University
1972 - Post-graduate degree in Haematology (University of Paris)
1972 - Post-graduate degree in Medical Parasitology (University of Paris)
1975 - Post-graduate degree in Immunology (University of Paris)

ACADEMIC APPOINTMENTS :

A - University
since1987 - Maître de conférences des Universités
1976 - Chef de Travaux Pratiques
1972 - Assistant

B - Hospital
1985 - Praticien hospitalier of Paris Hospitals
1975 - Assistant of Paris Hospitals
1972 - Resident of Paris Hospitals

C - Research Institute
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Ss-Dossier 224531 FR 01 ANTIG. HEPATIQUE P FALCIPARUM Inventeur: DEU002 DEVILLE PIERRE
N° D.I 186028 ANTIGENES HEPATIQUE DE P. FALCIPARUM

N° Ss-Dossier	Pays	N° Dépot	Date Dépot	Type de lien	Co-Propriétaire 1	Co-Propriétaire 2	Co-Propriétaire 3
.....	-- --	FRANCE	BFR/01543	9/02/1987	CNRS	INSTITUT PASTEUR	
224531	AT 01	AUTRICHE	EP89018545	9/02/1988	INSTITUT PASTEUR	CNRS	
224531	AU 01	AUSTRALIE	AU8931885	9/02/1988	INSTITUT PASTEUR	CNRS	
224531	BE 01	BELGIQUE	EP89018545	9/02/1988	INSTITUT PASTEUR	CNRS	
224531	CH 01	SUISSE	EP89018545	9/02/1988	INSTITUT PASTEUR	CNRS	
224531	DE 01	ALLEMAGNE	EP89018545	9/02/1988	INSTITUT PASTEUR	CNRS	
224531	EP 01	DEP.EUROP.	EP89018545	9/02/1988	INSTITUT PASTEUR	CNRS	
224531	ES 01	ESPAGNE	EP89018545	9/02/1988	INSTITUT PASTEUR	CNRS	
224531	FR 02	FRANCE	EP89018545	9/02/1988	INSTITUT PASTEUR	CNRS	
224531	GB 01	GR.BRETAG.	EP89018545	9/02/1988	INSTITUT PASTEUR	CNRS	
224531	IT 01	ITALIE	EP89018545	9/02/1988	INSTITUT PASTEUR	CNRS	
224531	JP 01	JAPON	JP501827	9/02/1988	INSTITUT PASTEUR	CNRS	
224531	LI 01	LIECHTENST	EP89018545	9/02/1988	INSTITUT PASTEUR	CNRS	
224531	LU 01	LUXEMBOURG	EP89018545	9/02/1988	INSTITUT PASTEUR	CNRS	
224531	PC 01	PCT	PCTFR8800076	9/02/1988	INSTITUT PASTEUR	P.M.S.V.	CNRS
224531	US 01	ETATS-UNIS	US275135	9/02/1988	INSTITUT PASTEUR	CNRS	
224531	US 02	ETATS-UNIS	US462512	7/06/1995 Division	INSTITUT PASTEUR	CNRS	
224531	US 03	ETATS-UNIS	US462062	7/06/1995 Division	INSTITUT PASTEUR	CNRS	
224531	US 04	ETATS-UNIS	US760000	3/12/1996 Division	INSTITUT PASTEUR	CNRS	

Ss-Dossier 224532 FR 01 METHODE SPOROZOITE-HEPATIQUE Inventeur: DEU002 DEVILLE PIERRE
N° D.I 189011 ANTIGENES DE SPOROZOITE DE P.FALCIPARUM

N° Ss-Dossier	Pays	N° Dépot	Date Dépot	Type de lien	Co-Propriétaire 1	Co-Propriétaire 2	Co-Propriétaire 3
.....	-- --	FRANCE	BFR04843	11/04/1989	INSTITUT PASTEUR	CNRS	
224532	AU 01	AUSTRALIE	AU8115790	11/04/1990	INSTITUT PASTEUR	CNRS	
224532	EP 01	DEP.EUROP.	EP9005945	11/04/1990	INSTITUT PASTEUR	CNRS	
224532	NZ 01	NVL.-ZELAND	NZ233378	11/04/1990	INSTITUT PASTEUR	CNRS	
224532	PT 01	PORTUGAL	PT93764	11/04/1990	INSTITUT PASTEUR	CNRS	
224532	US 01	ETATS-UNIS	US507215	11/04/1990	INSTITUT PASTEUR	CNRS	
224532	US 02	ETATS-UNIS	US754726	9/09/1991 Continu° in Part	INSTITUT PASTEUR	CNRS	
224532	US 03	ETATS-UNIS	US181597	10/08/1993	INSTITUT PASTEUR	CNRS	
224532	US 04	ETATS-UNIS	US242060	13/05/1994 Continu° in Part	INSTITUT PASTEUR	CNRS	
224532	US 05	ETATS-UNIS	US833098	14/04/1997 Division	INSTITUT PASTEUR	CNRS	
224532	US 06	ETATS-UNIS	US EN ATTENTE	13/03/1999 Continuation	INSTITUT PASTEUR	CNRS	
224532	EA 01	AFRQ-SUD	EA907811	12/04/1990	INSTITUT PASTEUR	CNRS	

Ss-Dossier 233621 FR 01 EPITOPE T DE P. FALCIPARUM Inventeur: DEU002 DEVILLE PIERRE
N° D.I 170014 EPITOPE T DE P. FALCIPARUM

N° Ss Dossier	Pays	N° Dépot	Date Dépot	Type de lien	Co-Propriétaire 1	Co-Propriétaire 2	Co-Propriétaire 3
.....	-- --	FRANCE	BFR91386	5/02/1991	INSTITUT PASTEUR	CNRS	
233621	AT 01	AUTRICHE	EP92058972	5/02/1992	INSTITUT PASTEUR	CNRS	
233621	BE 01	BELGIQUE	EP92058972	5/02/1992	INSTITUT PASTEUR	CNRS	
233621	CA 01	CANADA	CA2101924	5/02/1992	INSTITUT PASTEUR	CNRS	
233621	CH 01	SUISSE	EP92058972	5/02/1992	INSTITUT PASTEUR	CNRS	
233621	DE 01	ALLEMAGNE	EP92058972	5/02/1992	INSTITUT PASTEUR	CNRS	
233621	DK 01	DANEMARK	EP92058972	5/02/1992	INSTITUT PASTEUR	CNRS	
233621	EP 01	DEP.EUROP.	EP92058972	5/02/1992	INSTITUT PASTEUR	CNRS	
233621	ES 01	ESPAGNE	EP92058972	5/02/1992	INSTITUT PASTEUR	CNRS	
233621	FR 02	FRANCE	EP92058972	5/02/1992	INSTITUT PASTEUR	CNRS	
233621	GB 01	GR.BRETAG.	EP92058972	5/02/1992	INSTITUT PASTEUR	CNRS	
233621	GR 01	GRECE	EP92058972	5/02/1992	INSTITUT PASTEUR	CNRS	
233621	IT 01	ITALIE	EP92058972	5/02/1992	INSTITUT PASTEUR	CNRS	
233621	JP 01	JAPON	PCT/EP9200104	5/02/1992	INSTITUT PASTEUR		

233621 LI 01	LIECHTENST	EU93905 1972	5/02/1992		INSTITUT PASTEUR CNRS
233621 LU 01	LUXEMBOURG	EU9390 51972	5/02/1992		INSTITUT PASTEUR CNRS
233621 MC 01	MONACO	EU9390 51972	5/02/1992		INSTITUT PASTEUR CNRS
233621 NL 01	PAYS-BAS	EU9390 58972	5/02/1992		INSTITUT PASTEUR CNRS
233621 WC 01	PCT	PCTFR9200101	5/02/1992		INSTITUT PASTEUR
233621 SE 01	SUEDE	EU9390 58972	5/02/1992		INSTITUT PASTEUR CNRS
233621 US 01	ETATS-UNIS	US090327	5/02/1992		INSTITUT PASTEUR CNRS
233621 US 02	ETATS-UNIS	US467625	7/06/1995	Division	INSTITUT PASTEUR CNRS
233621 US 03	ETATS-UNIS	US637344	19/04/2001	Division	INSTITUT PASTEUR CNRS
233621 US 04	ETATS-UNIS	US900963	10/07/2001	Division	INSTITUT PASTEUR CNRS

Sa-Dossier 250068 FR 01 PROTEINE DE P. FALCIPARUM — Inventeur : DRU001 DRUILHE PIERRE
N° D.I 192053 PROTEINE DE P. FALCIPARUM

N° So-Dossier	Pays	N° Dépot	Date Dépôt	Type de lien	Co-Propriétaire 1	Co-Propriétaire 2	Co-Propriétaire 3
...... -- --	FRANCE	8F9212488	19/10/1992		INSTITUT PASTEUR		
250068 AT 01	AUTRICHE	EU9392 35842	18/10/1993		INSTITUT PASTEUR		
250068 BE 01	BELGIQUE	EU9392 35842	18/10/1993		INSTITUT PASTEUR		
250068 CH 01	SUISSE	EU9392 35842	18/10/1993		INSTITUT PASTEUR		
250068 DE 01	ALLEMAGNE	EU9392 35842	18/10/1993		INSTITUT PASTEUR		
250068 DK 01	DANEMARK	EU9392 35842	18/10/1993		INSTITUT PASTEUR		
250068 EP 01	ESP.EUROP.	EU9392 35842	18/10/1993		INSTITUT PASTEUR		
250068 EP 02	ESP.EUROP.	EU0400 39456	18/10/1993	Division	INSTITUT PASTEUR		
250068 ES 01	ESPAGNE	EU9392 35842	18/10/1993		INSTITUT PASTEUR		
250068 FR 02	FRANCE	EU9392 35842	18/10/1993		INSTITUT PASTEUR		
250068 GB 01	GR.BRETAG.	EU9392 35842	18/10/1993		INSTITUT PASTEUR		
250068 GR 01	GRECE	EU9392 35842	18/10/1993		INSTITUT PASTEUR		
250068 IE 01	IRLANDE	EU9392 35842	18/10/1993		INSTITUT PASTEUR		
250068 IT 01	ITALIE	EU9392 35842	18/10/1993		INSTITUT PASTEUR		
250068 JP 01	JAPON	PCTFR9301024	18/10/1993		INSTITUT PASTEUR		
250068 LI 01	LIECHTENST	EU9392 35842	18/10/1993		INSTITUT PASTEUR		
250068 LU 01	LUXEMBOURG	EU9392 35842	18/10/1993		INSTITUT PASTEUR		
250068 MC 01	MONACO	EU9392 35842	18/10/1993		INSTITUT PASTEUR		
250068 NL 01	PAYS-BAS	EU9392 35842	18/10/1993		INSTITUT PASTEUR		
250068 WC 01	PCT	PCTFR9301024	18/10/1993		INSTITUT PASTEUR		
250068 PT 01	PORTUGAL	EU9392 35842	18/10/1993		INSTITUT PASTEUR		
250068 SE 01	SUEDE	EU9392 35842	18/10/1993		INSTITUT PASTEUR		
250068 US 01	ETATS-UNIS	US416711	18/10/1993		INSTITUT PASTEUR		
250068 US 02	ETATS-UNIS	US356497	19/07/1999	Division	INSTITUT PASTEUR		
250068 US 03	ETATS-UNIS	US230741	11/09/2002	Continuation	INSTITUT PASTEUR		
250068 US 04	ETATS-UNIS	US294770	15/11/2002	Continuation	INSTITUT PASTEUR		
250068 US 05	ETATS-UNIS	US774602	10/02/2004	Continuation	INSTITUT PASTEUR		

Sa-Dossier 250136 FR 01 AG LSA3 DE P. FALCIPARUM — Inventeur : DRU001 DRUILHE PIERRE
N° D.I 194454 AG LSA3 DE P. FALCIPARUM

N° So-Dossier	Pays	N° Dépot	Date Dépot	Type de lien	Co-Propriétaire 1	Co-Propriétaire 2	Co-Propriétaire 3
...... -- --	FRANCE	8795071 07	11/06/1996		INSTITUT PASTEUR		
250136 AU 01	AUSTRALIE	AU6309596	11/06/1996		INSTITUT PASTEUR		
250136 CA 01	CANADA	CA2221929	11/06/1996		INSTITUT PASTEUR		
250136 EP 01	ESP.EUROP.	EU96921076	11/06/1996		INSTITUT PASTEUR		
250136 JP 01	JAPON	JP5027119714	11/06/1996		INSTITUT PASTEUR		
250136 WC 01	PCT	PCTFR9600834	11/06/1996		INSTITUT PASTEUR		
250136 US 01	ETATS-UNIS	US973462	11/06/1996		INSTITUT PASTEUR		
250136 US 02	ETATS-UNIS	US742036	20/12/2000	Division	INSTITUT PASTEUR		

Sa-Dossier 250260 US 01 COMPOSES LIPIDO-PEPTIDIQUES — Inventeur : DRU002 DRUILHE PIERRE
N° D.I 195044 COMPOSES LIPIDO-PEPTIDIQUES

N° Ss-Dossier	Pays	N° Dépot	Date Dépot	Type de lien	Co-Propriétaire 1	Co-Propriétaire 2	Co-Propriétaire 3
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250260 AL 01	ALBANIE	PCTFR0012794	8/12/2000		INSTITUT PASTEUR	UNIVERSITE DE LIL	
250260 AU 01	AUSTRALIE	PCTFR0012794	8/12/2000		INSTITUT PASTEUR	UNIVERSITE DE LIL	
250260 BB 01	BARBADE	PCTFR0012794	8/12/2000		INSTITUT PASTEUR	UNIVERSITE DE LIL	
250260 BG 01	BULGARIE	PCTFR0012794	8/12/2000		INSTITUT PASTEUR	UNIVERSITE DE LIL	
250260 BO 01	BOLIVIE	PCTFR0012794	8/12/2000		INSTITUT PASTEUR	UNIVERSITE DE LIL	
250260 BR 01	BRESIL	PCTFR0012794	8/12/2000		INSTITUT PASTEUR	UNIVERSITE DE LIL	
250260 BU 01	BIRMANIE	PCTFR0012794	8/12/2000		INSTITUT PASTEUR	UNIVERSITE DE LIL	
250260 BY 01	BELARUS	PCTFR0012794	8/12/2000		INSTITUT PASTEUR	UNIVERSITE DE LIL	
250260 CA 01	CANADA	CA2390347	8/12/2000		INSTITUT PASTEUR	UNIVERSITE DE LIL	
250260 CN 01	CHINE POP.	PCTFR0012794	8/12/2000		INSTITUT PASTEUR	UNIVERSITE DE LIL	
~~250260 CS 01~~	~~TCHECOSLOV~~	~~PCTFR0012794~~	~~8/12/2000~~		~~INSTITUT PASTEUR~~	~~UNIVERSITE DE LIL~~	
250260 CU 01	CUBA	PCTFR0012794	8/12/2000		INSTITUT PASTEUR	UNIVERSITE DE LIL	
250260 EP 01	ESP.EUROP.	EU009919747	8/12/2000		INSTITUT PASTEUR	UNIVERSITE DE LIL	
250260 GE 01	GEORGIE	PCTFR0012794	8/11/2000		INSTITUT PASTEUR	UNIVERSITE DE LIL	
250260 GH 01	GHANA	PCTFR0012794	8/11/2000		INSTITUT PASTEUR	UNIVERSITE DE LIL	
250260 HU 01	HONGRIE	PCTFR0012794	8/11/2000		INSTITUT PASTEUR	UNIVERSITE DE LIL	
250260 ID 01	INDONESIE	PCTFR0012794	8/11/2000		INSTITUT PASTEUR	UNIVERSITE DE LIL	
250260 IL 01	ISRAEL	PCTFR0012794	8/11/2000		INSTITUT PASTEUR	UNIVERSITE DE LIL	
250260 IN 01	INDE	PCTFR0012794	8/11/2000		INSTITUT PASTEUR	UNIVERSITE DE LIL	
250260 IS 01	ISLANDE	PCTFR0012794	8/11/2000		INSTITUT PASTEUR	UNIVERSITE DE LIL	
250260 JP 01	JAPON	PCTFR0012794	8/11/2000		INSTITUT PASTEUR	UNIVERSITE DE LIL	
250260 KE 01	KENYA	PCTFR0012794	8/11/2000		INSTITUT PASTEUR	UNIVERSITE DE LIL	
250260 KP 01	COREE NORD	PCTFR0012794	8/11/2000		INSTITUT PASTEUR	UNIVERSITE DE LIL	
250260 KR 01	COREE SUD	PCTFR0012794	8/11/2000		INSTITUT PASTEUR	UNIVERSITE DE LIL	
250260 KZ 01	KAZACKSTAN	PCTFR0012794	8/11/2000		INSTITUT PASTEUR	UNIVERSITE DE LIL	
250260 MA 01	MAROC	PCTFR0012794	8/11/2000		INSTITUT PASTEUR	UNIVERSITE DE LIL	
250260 MG 01	MADAGASCAR	PCTFR0012794	8/12/2000		INSTITUT PASTEUR	UNIVERSITE DE LIL	
250260 MX 01	MEXIQUE	PCTFR0012794	8/12/2000		INSTITUT PASTEUR	UNIVERSITE DE LIL	
250260 MY 01	MALAISIE	PCTFR0012794	8/12/2000		INSTITUT PASTEUR	UNIVERSITE DE LIL	
250260 NZ 01	NVL.ZELAND	PCTFR0012794	8/12/2000		INSTITUT PASTEUR	UNIVERSITE DE LIL	
250260 OA 01	O.A.P.I.	PCTFR0012794	8/12/2000		INSTITUT PASTEUR	UNIVERSITE DE LIL	
250260 PC 01	PCT	PCTFR0012794	8/12/2000		INSTITUT PASTEUR	UNIVERSITE DE LIL	
250260 PH 01	PHILIPPINE	PCTFR0012794	8/12/2000		INSTITUT PASTEUR	UNIVERSITE DE LIL	
250260 PL 01	POLOGNE	PCTFR0012794	8/12/2000		INSTITUT PASTEUR	UNIVERSITE DE LIL	
250260 RO 01	ROUMANIE	PCTFR0012794	8/12/2000		INSTITUT PASTEUR	UNIVERSITE DE LIL	
250260 SG 01	SINGAPOUR	PCTFR0012794	8/12/2000		INSTITUT PASTEUR	UNIVERSITE DE LIL	
250260 SX 01	SARAWAK	PCTFR0012794	8/12/2000		INSTITUT PASTEUR	UNIVERSITE DE LIL	
250260 SL 01	SIER.LEONE	PCTFR0012794	8/12/2000		INSTITUT PASTEUR	UNIVERSITE DE LIL	
250260 SQ 01	SLOVAQUIE	PCTFR0012794	8/12/2000		INSTITUT PASTEUR	UNIVERSITE DE LIL	
250260 SU 01	FED RUSSIE	PCTFR0012794	8/12/2000		INSTITUT PASTEUR	UNIVERSITE DE LIL	
250260 TH 01	THAILANDE	PCTFR0012794	8/12/2000		INSTITUT PASTEUR	UNIVERSITE DE LIL	
250260 TX 01	TRAGBERI	PCTFR0012794	8/12/2000		INSTITUT PASTEUR	UNIVERSITE DE LIL	
250260 TR 01	TURQUIE	PCTFR0012794	8/12/2000		INSTITUT PASTEUR	UNIVERSITE DE LIL	
250260 US 03	ETATS-UNIS	US161750	8/12/2000		INSTITUT PASTEUR	UNIVERSITE DE LIL	
250260 VN 01	VIET-NAM	PCTFR0012794	8/12/2000		INSTITUT PASTEUR	UNIVERSITE DE LIL	
250260 YU 01	CROATIE	PCTFR0012794	8/12/2000		INSTITUT PASTEUR	UNIVERSITE DE LIL	
250260 ZA 01	AFRQ-SUD	PCTFR0012794	8/12/2000		INSTITUT PASTEUR	UNIVERSITE DE LIL	

Ss-Dossier 250260 US 03 COMPOSES LIPIDO-PEPTIDIQUES Inventeur: DRU003 DRUILHE PIERRE
I° D.I 199044 COMPOSES LIPIDO-PEPTIDIQUES

N° Ss-Dossier	Pays	N° Dépot	Date Dépot	Type de lien	Co-Propriétaire 1	Co-Propriétaire 2	Co-Propriétaire 3
------- -- --	ETATS-UNIS	US732754	11/12/2000		INSTITUT PASTEUR	UNIVERSITE DE LIL	

Ss-Dossier 250260 US 04 COMPOSES LIPIDO-PEPTIDIQUES Inventeur: DRU003 DRUILHE PIERRE

N° D.I 192044 COMPOSES LIPIDO-PEPTIDIQUES

N° Ss Dossier	Pays	N° Dépôt	Date Dépôt	Type de lien	Co-Propriétaire 1	Co-Propriétaire 2	Co-Propriétaire 3
-- --	ETATS UNIS	US206515	29/07/2002	Division	INSTITUT PASTEUR	UNIVERSITE ET [illegible]	

Ss-Dossier 250300 EP 01 LSA 3 et adjuvants Inventeur: DRU002 DRUILHE PIERRE
N° D.I 200064 LSA 3 et adjuvants

N° Ss-Dossier	Pays	N° Dépôt	Date Dépôt	Type de lien	Co-Propriétaire 1	Co-Propriétaire 2	Co-Propriétaire 3
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250300 CA 01	CANADA	PCTFR0112369	23/10/2001		INSTITUT PASTEUR	SMITH KLINE BEECH	
250300 EP 02	DEP.EUROP.	EU01980374 9	23/10/2001		INSTITUT PASTEUR	SMITH KLINE BEECH	
250300 JP 01	JAPON	JP302540205	23/10/2001		INSTITUT PASTEUR	SMITH KLINE BEECH	
250300 PC 01	PCT	PCTFR0112369	23/10/2001		INSTITUT PASTEUR	SMITH KLINE BEECH	
250300 US 01	ETATS-UNIS	PCTFR0112369	23/10/2001		INSTITUT PASTEUR	SMITH KLINE BEECH	

Ss-Dossier 250322 CA 01 Antigènes de Plasmodium falciparum Inventeur: DRU002 DRUILHE PIERRE
N° D.I 201031 Antigènes de Plasmodium falciparum

N° Ss-Dossier	Pays	N° Dépôt	Date Dépôt	Type de lien	Co-Propriétaire 1	Co-Propriétaire 2	Co-Propriétaire 3
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250322 AL 01	ALBANIE	PCTFR0201637	15/05/2002		INSTITUT PASTEUR		
250322 AU 01	AUSTRALIE	PCTFR0201637	15/05/2002		INSTITUT PASTEUR		
250322 BB 01	BARBADE	PCTFR0201637	15/05/2002		INSTITUT PASTEUR		
250322 BG 01	BULGARIE	PCTFR0201637	15/05/2002		INSTITUT PASTEUR		
250322 BO 01	BOLIVIE	PCTFR0201637	15/05/2002		INSTITUT PASTEUR		
250322 BR 01	BRESIL	PCTFR0201637	15/05/2002		INSTITUT PASTEUR		
250322 BU 01	BIRMANIE	PCTFR0201637	15/05/2002		INSTITUT PASTEUR		
250322 BY 01	BELARUS	PCTFR0201637	15/05/2002		INSTITUT PASTEUR		
250322 CA 03	CANADA	CA2381917	15/05/2002		INSTITUT PASTEUR		
250322 CN 01	CHINE POP.	PCTFR0201637	15/05/2002		INSTITUT PASTEUR		
250322 CS 01	TCHECOSLOV	PCTFR0201637	15/05/2002		INSTITUT PASTEUR		
250322 CU 01	CUBA	PCTFR0201637	15/05/2002		INSTITUT PASTEUR		
250322 EP 01	DEP.EUROP.	EU02732872 1	15/05/2002		INSTITUT PASTEUR		
250322 GE 01	GEORGIE	PCTFR0201637	15/05/2002		INSTITUT PASTEUR		
250322 GH 01	GHANA	PCTFR0201637	15/05/2002		INSTITUT PASTEUR		
250322 HU 01	HONGRIE	PCTFR0201637	15/04/2002		INSTITUT PASTEUR		
250322 ID 01	INDONESIE	PCTFR0201637	15/05/2002		INSTITUT PASTEUR		
250322 IL 01	ISRAEL	PCTFR0201637	15/05/2002		INSTITUT PASTEUR		
250322 IN 01	INDE	PCTFR0201637	15/05/2002		INSTITUT PASTEUR		
250322 IS 01	ISLANDE	PCTFR0201637	15/05/2002		INSTITUT PASTEUR		
250322 JP 01	JAPON	PCTFR0201637	15/05/2002		INSTITUT PASTEUR		
250322 KE 01	KENYA	PCTFR0201637	15/05/2002		INSTITUT PASTEUR		
250322 KP 01	COREE NORD	PCTFR0201637	15/05/2002		INSTITUT PASTEUR		
250322 KR 01	COREE SUD	PCTFR0201637	15/05/2002		INSTITUT PASTEUR		
250322 KZ 01	KAZACKSTAN	PCTFR0201637	15/05/2002		INSTITUT PASTEUR		
250322 MA 01	MAROC	PCTFR0201637	15/05/2002		INSTITUT PASTEUR		
250322 MG 01	MADAGASCAR	PCTFR0201637	15/05/2002		INSTITUT PASTEUR		
250322 MX 01	MEXIQUE	PCTFR0201637	15/05/2002		INSTITUT PASTEUR		
250322 MY 01	MALAISIE	PCTFR0201637	16/05/2002		INSTITUT PASTEUR		
250322 NZ 01	NVL.ZELAND	PCTFR0201637	15/05/2002		INSTITUT PASTEUR		
250322 OA 01	O.A.P.I.	PCTFR0201637	15/05/2002		INSTITUT PASTEUR		
250322 PC 01	PCT	PCTFR0201637	15/05/2002		INSTITUT PASTEUR		
250322 PH 01	PHILIPPINE	PCTFR0201637	15/05/2002		INSTITUT PASTEUR		
250322 PL 01	POLOGNE	PCTFR0201637	15/05/2002		INSTITUT PASTEUR		
250322 RO 01	ROUMANIE	PCTFR0201637	15/05/2002		INSTITUT PASTEUR		
250322 SG 01	SINGAPOUR	PCTFR0201637	15/05/2002		INSTITUT PASTEUR		
250322 SK 01	SARAWAK	PCTFR0201637	15/05/2002		INSTITUT PASTEUR		
250322 SL 01	SIER.LEONE	PCTFR0201637	15/05/2002		INSTITUT PASTEUR		

250322 SQ 01	SLOVAQUIE	PCTFR0201637	15/05/2002		INSTITUT PASTEUR	
250322 SU 01	FED RUSSIE	PCTFR0201637	15/05/2002		INSTITUT PASTEUR	
250322 TH 01	THAILANDE	PCTFR0201637	15/05/2002		INSTITUT PASTEUR	
250322 TK 01	TRANSKEI	PCTFR0201637	15/05/2002		INSTITUT PASTEUR	
250322 TN 01	TUNISIE	PCTFR0201637	15/05/2002		INSTITUT PASTEUR	
250322 TR 01	TURQUIE	PCTFR0201637	15/05/2002		INSTITUT PASTEUR	
250322 US 01	ETATS-UNIS	US[illegible]	15/05/2002		INSTITUT PASTEUR	
250322 VN 01	VIET NAM	PCTFR0201637	15/05/2002		INSTITUT PASTEUR	
250322 YU 01	CROATIE	PCTFR0201637	15/05/2002		INSTITUT PASTEUR	
250322 ZA 01	AFRO-SUD	PCTFR0201637	15/05/2002		INSTITUT PASTEUR	

Sous-Dossier 250322 CH 02 Antigènes de Plasmodium falciparum Inventeurs: [illegible]
NL U.4.201011 Antigènes de Plasmodium falciparum

N° de Dossier	Pays	N° Dépôt	Date Dépôt	Type de lien	Co-Propriétaire 1	Co-Propriétaire 2 Co-Propriétaire 3
	CANADA	CA2316958	21/05/2001		INSTITUT PASTEUR	
250322 AL 01	ALBANIE	PCTFR0201637	15/05/2002		INSTITUT PASTEUR	
250322 AU 01	AUSTRALIE	PCTFR0201637	15/05/2002		INSTITUT PASTEUR	
250322 BB 01	BARBADE	PCTFR0201637	15/05/2002		INSTITUT PASTEUR	
250322 BG 01	BULGARIE	PCTFR0201637	15/05/2002		INSTITUT PASTEUR	
250322 BO 01	BOLIVIE	PCTFR0201637	15/05/2002		INSTITUT PASTEUR	
250322 BR 01	BRESIL	PCTFR0201637	15/05/2002		INSTITUT PASTEUR	
250322 BU 01	BIRMANIE	PCTFR0201637	15/05/2002		INSTITUT PASTEUR	
250322 BY 01	BELARUS	PCTFR0201637	15/05/2002		INSTITUT PASTEUR	
250322 CA 01	CANADA	CA2392977	15/05/2002		INSTITUT PASTEUR	
250322 CN 01	CHINE POP.	PCTFR0201637	15/05/2002		INSTITUT PASTEUR	
250322 CS 01	TCHECOSLOV	PCTFR0201637	15/05/2002		INSTITUT PASTEUR	
250322 CU 01	CUBA	PCTFR0201637	15/05/2002		INSTITUT PASTEUR	
250322 EP 01	DEP.EUROP.	EU02732672[illegible]	15/05/2002		INSTITUT PASTEUR	
250322 GE 01	GEORGIE	PCTFR0201637	15/05/2002		INSTITUT PASTEUR	
250322 GH 01	GHANA	PCTFR0201637	15/05/2002		INSTITUT PASTEUR	
250322 HU 01	HONGRIE	PCTFR0201637	15/05/2002		INSTITUT PASTEUR	
250322 ID 01	INDONESIE	PCTFR0201637	15/05/2002		INSTITUT PASTEUR	
250322 IL 01	ISRAEL	PCTFR0201637	15/05/2002		INSTITUT PASTEUR	
250322 IN 01	INDE	PCTFR0201637	15/05/2002		INSTITUT PASTEUR	
250322 IS 01	ISLANDE	PCTFR0201637	15/05/2002		INSTITUT PASTEUR	
250322 JP 01	JAPON	PCTFR0201637	15/05/2002		INSTITUT PASTEUR	
250322 KE 01	KENYA	PCTFR0201637	15/05/2002		INSTITUT PASTEUR	
250322 KP 01	COREE NORD	PCTFR0201637	15/05/2002		INSTITUT PASTEUR	
250322 KR 01	COREE SUD	PCTFR0201637	15/05/2002		INSTITUT PASTEUR	
250322 KZ 01	KAZACKSTAN	PCTFR0201637	15/05/2002		INSTITUT PASTEUR	
250322 MA 01	MAROC	PCTFR0201637	15/05/2002		INSTITUT PASTEUR	
250322 MG 01	MADAGASCAR	PCTFR0201637	15/05/2002		INSTITUT PASTEUR	
250322 MX 01	MEXIQUE	PCTFR0201637	15/05/2002		INSTITUT PASTEUR	
250322 MY 01	MALAISIE	PCTFR0201637	15/05/2002		INSTITUT PASTEUR	
250322 NZ 01	NVL.ZELAND	PCTFR0201637	15/05/2002		INSTITUT PASTEUR	
250322 OA 01	O.A.P.I.	PCTFR0201637	15/05/2002		INSTITUT PASTEUR	
250322 PC 01	PCT	PCTFR0201637	15/05/2002		INSTITUT PASTEUR	
250322 PH 01	PHILIPPINE	PCTFR0201637	15/05/2002		INSTITUT PASTEUR	
250322 PL 01	POLOGNE	PCTFR0201637	15/05/2002		INSTITUT PASTEUR	
250322 RO 01	ROUMANIE	PCTFR0201637	15/05/2002		INSTITUT PASTEUR	
250322 SG 01	SINGAPOUR	PCTFR0201637	15/05/2002		INSTITUT PASTEUR	
250322 SK 01	SARAWAK	PCTFR0201637	15/05/2002		INSTITUT PASTEUR	
250322 SL 01	SIER.LEONE	PCTFR0201637	15/05/2002		INSTITUT PASTEUR	
250322 SQ 01	SLOVAQUIE	PCTFR0201637	15/05/2002		INSTITUT PASTEUR	
250322 SU 01	FED RUSSIE	PCTFR0201637	15/05/2002		INSTITUT PASTEUR	
250322 TH 01	THAILANDE	PCTFR0201637	15/05/2002		INSTITUT PASTEUR	

250322 TK 01 TRANSKEI	PCTFR0201637	15/05/2002		INSTITUT PASTEUR		
250323 TN 01 TUNISIE	PCTFR0201637	15/05/2002		INSTITUT PASTEUR		
250324 TR 01 TURQUIE	PCTFR0201637	15/05/2002		INSTITUT PASTEUR		
250325 US 01 ETATS-UNIS	US7212531	15/05/2002		INSTITUT PASTEUR		
250327 VN 01 VIET-NAM	PCTFR0201637	15/05/2002		INSTITUT PASTEUR		
250327 YU 01 COUNTRY	PCTFR0201637	15/05/2002		INSTITUT PASTEUR		
250327 ZA 01 AFRQ-SUD	PCTFR0201637	15/05/2002		INSTITUT PASTEUR		

So-Dossier 250321 CA 04 Antigènes de Plasmodium falciparum Inventeur: DRU002 DRUILHE PIERRE
N° D.I 201031 Antigènes de Plasmodium falciparum

N° So-Dossier	Pays	N° Dépot	Date Dépot	Type de lien	Co-Propriétaire 1	Co-Propriétaire 2	Co-Propriétaire 3
-------	-- --	CANADA	CA2383977	15/05/2002		INSTITUT PASTEUR	

So-Dossier 250369 GB 01 Anticorps recombinants de P.falciparum Inventeur: DRU002 DRUILHE PIERRE
N° D.I 202046 Anticorps recombinants de P.falciparum

N° So-Dossier	Pays	N° Dépot	Date Dépot	Type de lien	Co-Propriétaire 1	Co-Propriétaire 2	Co-Propriétaire 3
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250369 AU 01	AUSTRALIE	AU2002226106	16/01/2002			DANISH TECHNOLOGI	INSTITUT PASTEUR
250369 BR 01	BRESIL	BR0211943#	16/08/2002			DANISH TECHNOLOGI	INSTITUT PASTEUR
250369 CA 01	CANADA	CA2450890	16/08/2002			DANISH TECHNOLOGI	INSTITUT PASTEUR
250369 EP 01	OFF.EUROP.	EU0276054A6	16/08/2002			DANISH TECHNOLOGI	INSTITUT PASTEUR
250369 JP 01	JAPON	JP2004-521375	16/08/2002			DANISH TECHNOLOGI	INSTITUT PASTEUR
250369 PC 01	PCT	PCTIBC281095	16/08/2002			DANISH TECHNOLOGI	INSTITUT PASTEUR
250369 US 01	ETATS-UNIS	US486703	16/08/2002			DANISH TECHNOLOGI	INSTITUT PASTEUR

So-Dossier 250381 US 01 Composition immunogène dérivée de RSP3 Inventeur: DRU002 DRUILHE PIERRE
N° D.I 202101 Composition immunogène dérivée de RSP3

N° So-Dossier	Pays	N° Dépot	Date Dépot	Type de lien	Co-Propriétaire 1	Co-Propriétaire 2	Co-Propriétaire 3
-------	-- --	ETATS-UNIS	US256770	15/11/2002 Contin* in Part		INSTITUT PASTEUR	

So-Dossier 250424 EP 01 Antibodies effective at killing P.falci Inventeur: DRU002 DRUILHE PIERRE
N° D.I 203044 Antibodies effective at killing P.falci.
d° D.I 202103 Composition immunogène dérivée de RSP3

N° So-Dossier	Pays	N° Dépot	Date Dépot	Type de lien	Co-Propriétaire 1	Co-Propriétaire 2	Co-Propriétaire 3
-------	-- --	OFF.EUROP.	EP03936739	24/10/2003		INSTITUT PASTEUR	
250424 PC 01	PCT	PCTEP2004012959	22/10/2004			INSTITUT PASTEUR	

So-Dossier 250426 US 01 MSP-3 CLUSD malaria vaccine candidate Inventeur: DRU002 DRUILHE PIERRE
N° D.I 203060 MSP-3 CLUSD malaria vaccine candidate

N° So-Dossier	Pays	N° Dépot	Date Dépot	Type de lien	Co-Propriétaire 1	Co-Propriétaire 2	Co-Propriétaire 3
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250426 PC 01	PCT	PCTEP2004012910	22/10/2004			INSTITUT PASTEUR	

So-Dossier 250431 EP 01 Nouvel antigène de P.falciparum : LSA-5 Inventeur: DZI002 DRUILHE PIERRE
N° D.I 203034 Nouvel antigène de P.falciparum : LSA-5
d° D.I 202121 Nouvel antigène de P.falciparum : LSA-5
d° D.I 2020068 Nouvel antigène de P.falciparum

N° So-Dossier	Pays	N° Dépot	Date Dépot	Type de lien	Co-Propriétaire 1	Co-Propriétaire 2	Co-Propriétaire 3
-------	-- --	OFF.EUROP.	EP03293586	15/12/2003		INSTITUT PASTEUR	

So-Dossier 250431 PC 01 Nouvel antigène de P.falciparum : LSA-5 Inventeur: DRU002 DRUILHE PIERRE
N° D.I 203034 Nouvel antigène de P.falciparum : LSA-5
N° D.I 202121 Nouvel antigène de P.falciparum : LSA-5
N° D.I 2020068 Nouvel antigène de P.falciparum

N° So-Dossier	Pays	N° Dépot	Date Dépot	Type de lien	Co-Propriétaire 1	Co-Propriétaire 2	Co-Propriétaire 3
-------	-- --	PCT	PCTEP2004014848	15/12/2004		INSTITUT PASTEUR	

Sa-Dossier 250415 EP 01 Modèle souris Inventeur: GRU002 GRUTLER PIERRE

N° D.I 203131 Development of an improved mouse model

N° Sa-Dossier	Pays	N° Dépot	Date Dépot	Type de lien	Co-Propriétaire 1	Co-Propriétaire 2	Co-Propriétaire 3
------- -- --	DEP.EUROP.	EU04290066 2	9/01/2004		INSTITUT PASTEUR		
250135 PC 01	PCT	PCTEP2005000547	7/01/2005		INSTITUT PASTEUR		

Sa-Dossier 250453 EP 01 Major improvement in human hepatocytes Inventeur: GRU002 GRUTLER PIERRE

N° D.I 202100 Major improvement in human hepatocytes

N° Sa-Dossier	Pays	N° Dépot	Date Dépot	Type de lien	Co-Propriétaire 1	Co-Propriétaire 2	Co-Propriétaire 3
------- -- --	DEP.EUROP.	EU0430C6654	9/01/2004		INSTITUT PASTEUR	INSERM	
250453 PC 01	PCT	PCTEP2005000546	7/01/2005		INSTITUT PASTEUR	INSERM	

Sa-Dossier 250458 US 01 Antibodies against malaria Inventeur: GRU002 GRUTLER-PIERRE

N° D.I 204076 Antibodies against malaria

N° Sa-Dossier	Pays	N° Dépot	Date Dépot	Type de lien	Co-Propriétaire 1	Co-Propriétaire 2	Co-Propriétaire 3
------- -- --	ETATS-UNIS	US598062	2/08/2004		INSTITUT PASTEUR		

** Fin d'Edition **

DOCUMENT I

Initiative for Vaccine Research (IVR)

HIV/AIDS

Disease burden. WHO and UNAIDS have estimated that at the end of 2002 the number of adults and children living with HIV/AIDS worldwide will have reached 42 million (AIDS Epidemic Update 2002). It is also estimated that, during 2002, 5 million people (including 800 000 children aged under 15 years) became infected and 3.1 million have died of the disease (WHO, 2002). Human Immunodeficiency viruses belong to the Retroviridae family, lentivirus genus. Two types have been desbribed: HIV-1 and HIV-2. HIV infections are now almost equally distributed between men and women, with an estimated 17.6 million women aged 15-49 living with HIV/AIDS. The vast majority of people living with HIV/AIDS are not aware that they are carrying the virus. Deaths in women also continue to increase, accounting for an estimated 48% of adult deaths due to HIV in 2002. HIV/AIDS is the leading cause of death in sub-Saharan Africa and the fourth biggest killer worldwide.

Some regional trends can be observed. During 2002, AIDS killed 2.4 million people in sub-Saharan Africa while an estimated 3.5 million people have been newly infected with HIV, bringing the number of Africans living with HIV/AIDS to 29.4 million. sub-Saharan Africa remains the hardest-hit region, accounting for 68% of the 5 million people infected worldwide with HIV during 2001, 71% of the people living with HIV/AIDS and 77% of AIDS deaths.

The estimated number of adults and children living with HIV in Latin America and the Caribbean at the end of 2002 was 1.5 million. While in some countries HIV infections remain concentrated mainly in men who have unprotected sex with other men and injecting drug users, others are experiencing increasing rates of heterosexual transmission. AIDS mortality has been reduced in some countries thanks to antiretroviral therapy.

Eastern Europe and Central Asia continue to experience the world's fastest-growing HIV/AIDS epidemic. During 2002, there were an estimated 250 000 new infections, bringing the number of people living with HIV/AIDS to 1.2 million. Most of the infections continue to occur among injecting drug users.

In North Africa and the Middle East, the number of people living with HIV/AIDS now totals 550 000. While HIV prevalence continues to be low in most countries in the region, an increasing number of HIV infections have been detected in several countries, particularly in countries experiencing complex emergencies.

During 2002, highly active antiretroviral therapy has continued to reduce progression to AIDS, deaths and HIV transmission from mother to child in the industrialized countries of North America, Western Europe and the Pacific. However, these successes in treatment and care are not being matched by progress in prevention. During 2002, 76 000 individuals became infected with HIV in industrialized countries, where an estimated 1.6 million people are now living with HIV. New evidence of rising HIV infection rates is emerging, particularly in marginalized communities.

Diarrhoeal diseases
Rotavirus
Enterotoxigenic Escherichia coli
Shigella
Cholera
Typhoid
Calciviruses

Acute respiratory infections
Streptococcus pneumoniae
Respiratory syncytial virus
Parainfluenza virus type 3
Influenza

Tuberculosis
Buruli Ulcer
Chlamydia Trachomatis
HIV/AIDS
Herpes simplex virus type 2
Malaria
Leishmaniasis
Schistosomiasis
Dengue
Japanese Encephalitis
Tick-Borne Encephalitis
West Nile Encephalitis
Meningitis N. meningitidis
Hepatitis C
Hepatitis E
Helicobacter pylori
Human Papilloma Virus
Epstein Barr Virus
Poliomyelitis
Measles
Rabies
Group A Streptococcus
Group B Streptococcus
Leptospirosis

R&D status for new vaccines and biologicals

Vaccines. While HIV/AIDS continues to spread in all regions of the world, there are positive signs. In both industrialized and developing countries, an increasing number of HIV-positive people can live longer and healthier lives thanks to antiretroviral therapies. Large-scale prevention programmes have reversed epidemic trends in some Asian countries. The estimated number of new infections in most Central/East/West African countries seem to decline, and there are some initial indications that the epidemics might have peaked in southern Africa. But above all, a new determination to fight the epidemic has emerged following the United Nations General Assembly Special Session on HIV/AIDS in July 2001. However, despite these encouraging trends, a preventive vaccine is more than ever needed, in particular for developing countries. The development of a safe and effective vaccine is hampered by the high genetic variability of HIV, the paucity of knowledge on the immune mechanisms of protection, the absence of relevant and predictive animal models, and the complexity of the implementation of efficacy trials, especially in developing countries . Several vaccine candidates have been tested over the past 15 years and are in the pipeline for further human testing . The first Phase I trial of an HIV vaccine

was conducted in the US in 1987. Since then, over 30 candidate vaccines have been tested in over 80 Phase I/II clinical trials, involving over 10 000 healthy human volunteers (adults and infants). The majority of these trials have been conducted in the US and Europe, however, trials have also been conducted in developing countries (Brazil, China, Cuba, Haiti, Kenya, Thailand, Trinidad and Uganda). The effort to develop and evaluate HIV vaccines must increase, especially in Africa. This effort will be strengthened by the African Aids Vaccine Programme (AAVP), which has been recently established following an initiative in WHO and UNAIDS. Only two efficacy trials have been started so far, both using the same approach of a monomeric gp120, one in the United-States (with sites in Canada and in the Netherlands), the other in Thailand (Vaxgen/CDC). Definite results from the USA trial have been reported in March 2003. The study did not show a statistically significant reduction of HIV infection within the study population as a whole, which was the primary endpoint of the trial. However, the study did show a statistically significant reduction of HIV infection in certain vaccinated groups. Protection appeared to correlate with the higher level of vaccine-induced neutralizing antibodies observed in these groups, according to Vaxgen. A third efficacy trial of a recombinant canarypox HIV vector prime-gp120 boost vaccine in heterosexual volunteers in Thailand is expected to start late 2003 (WRAIR/NIH/Vaxgen/Aventis Pasteur). Other interesting approaches based on DNA prime and recombinant poxviruses (MVA, fowlpox) boost are being tested in humans. Recombinant adenoviruses represent another promising approach, already tested in Phase I in humans. Other candidate vaccines include recombinant Salmonella (IAVI/Institute for Human Virology, University of Maryland, USA), VEE (Alphavax, USA), subunit HIV proteins (GSK, Center for Genetic Engineering and Biotechnology (CIGB) in Cuba, among others), DNA vaccines (Wyeth/University of Pennsylvania, among others) or peptides (Wyeth/Duke University). The development of a safe, effective, and affordable HIV vaccine remains the scientific and public health challenge of this new century. However, it is urgent that the availability and affordability of a safe and efficient HIV vaccine should by any means strongly encourage, strengthen, and expand the efforts of traditional prevention against HIV infection proven to be efficient in some countries.

WHO-UNAIDS HIV Vaccine Initiative
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Herpes simplex virus type 2

Disease burden. HSV-2 prevalence is increasing worldwide. There is now ample evidence that *Herpes simplex* virus type 2 (HSV-2) infection, the most common cause of genital ulcers worldwide, is a major cofactor favoring HIV infection. HSV-2 prevalence is generally higher in developing than in developed countries and in urban than rural areas. The HSV-2 prevalence in developing countries, although very high, varies widely according to the countries, the gender, urban versus rural areas, ranging from 2-74%, very few being available from Asian and South American countries. HSV-2 incidence data are scarce. In the community-based survey, HSV-2 prevalence increased with age until 25 years, leveled off at 50% in both genders. The same independent predictors of HSV-2 infection were identified in both genders: older age, higher lifetime number of sexual partners, positive HIV serology, and positive *Treponema pallidum* hemagglutination serology. In Bangladesh a study conducted in truck drivers showed a high HSV-2 prevalence of disease were HSV-2 (25.8%), compared to serological syphilis (5.7%), gonorrhea (2.1%), chlamydia (0.8%). In New Zealand, increased rates of HSV-2 acquisition after age 21 may be due to a higher prevalence of infection in the pool of potential partners encountered during the third decade of life. Factors related to partner choice may have more influence on the risk of HSV-2 infection than the number of sexual partners alone. Overall prevalence is higher in women compared with men, especially among the young , and rates up to 40 % have been reported among women aged 15-19 in Kisumu (Kenya). Prevalence is higher in the USA (22% in adults) compared to Europe (generally lower than 15%). It is now estimated that in the USA alone, 40 to 60 million people are HSV-2-infected, with 2 million incident cases per year and 600 000 clinical cases. The clinical spectrum of HSV-2 includes primary infection, a first episode of genital herpes and recurrent episodes of clinical disease (4-5 per year). In addition, subclinical infection may be associated with infectious viral shedding. The proportion of infections which are sympomatic is estimated to be between 13 and 37%, although this is higher in HIV positive individuals. The risk of neonatal herpes is very low (less than 3%) among HIV-negative pregnant women living in developed countries, but few data are available on neonatal herpes in developing countries. A recent meta-analysis of thirty-one studies addressing the risk of HIV infection in HSV-2-seropositive persons was performed. For nine cohort and nested case-control studies that documented HSV-2 infection before HIV acquisition, the risk estimate was 2.1 (95% confidence interval, 1.4-3.2). Thus, the attributable risk percentage of HIV to HSV-2 was 52%, and the population attributable risk percentage was 19% in populations with 22% HSV-2 prevalence but increased to 47% in populations with 80% HSV-2 prevalence. For 22 case-control and cross-sectional studies, the risk estimate was 3.9 (95% confidence interval, 3.1-5.1), but the temporal sequence of the two infections cannot be documented. Control strategies for HSV-2 need to be incorporated into control of sexually transmitted infections as a strategy for HIV prevention.

In developed countries, acquisition of HSV-1 in childhood has decreased as HSV-2 seroprevalence has increased, suggesting a possible protective effect of HSV-1 against HSV-2 acquisition. However, studies have shown discrepant results in this respect. Although HSV-1 does not seem to modify the risk of HSV-2 acquisition , it seems to increase the proportion of asymptomatic seroconversions and, in one study, to increase the rate of HSV-2 shedding. Infection with HSV-1 in childhood is almost universal in developing countries, where HSV-2 prevalance is very high, and this confirms that HSV-1 provides limited protection against HSV-2 infection.

Vaccines. Herpesvirus 2 belongs to the enveloped *Herpesviridae* family. The first generation of vaccines was recombinant subunit viral glycoproteins. Chiron developed a two-component (30 mg of both gB2 and gD2 glycoproteins) subunit vaccine formulated in MF59 adjuvant and SmithKline Beecham a monovalent vaccine (gD2) formulated in alum + monophosphoryl lipid A (Corixa). The Chiron vaccine induced very high antibody titres, and efficacy in women for the first 5 months was 26%, but this protection against

infection was not sustained. Chiron doesn't have an active HSV-2 vaccine at present. The Phase III trials of the vaccine developed by GlaxoSmithKline (glycoprotein gD2 formulated with adjuvant) showed limited efficacy, depending on gender and previous exposure to HSV-1. Indeed, these trials showed a 73% and 74% efficacy (P=0.01 and 0.02, respectively) against genital herpes disease in HSV-1- and HSV-2-negative women. Trends towards protection in women against HSV infection were also seen in both studies (39-48% efficacy), although not statistically significant. The main disadvantages of this vaccine are the apparent failure to improve on protection provided by HSV-1 infection and the need for frequent administration to boost host immunity. Further efficacy trials of this vaccine, which has already been administrated in about 7 500 individuals, are pending in collaboration with NIAID. A novel HSV-2 candidate vaccine has been developed by Cantab Pharmaceuticals (now Xenova)/GlaxoSmithKline based on a genetically Disabled Infectious Single Cycle (DISC, glycoprotein H-deleted, ICP8 gene mutation) replicative vaccine, which is believed could have higher efficacy than previous vaccines. This new candidate vaccine has been tested in Phase II trials in the US and UK, showing good tolerance and inducing neutralizing antibodies and CTL in 83% of the vaccine recipients. Nevertheless, no difference in time to recurrence was observed in this therapeutic candidate vaccine in HSV-2 seropositive symptomatic, and no difference was recorded in shedding. Therefore, Xenova (without GSK) is refocusing their programme on prophylactic applications for their DISC vaccine. One complexity of evaluating protection against infection induced by the DISC vaccine is that, because of the similarity of the disabled virus and wild HSV-2, it will not be possible to distinguish natural infection from vaccine-induced immunity. Another live, replication-impaired vaccine is currently under development by Avant Immunotherapeutics. AuRx, Inc concentrate on live genetically-attenuated replication-competent vaccines and PowderJect and Merck on DNA vaccine formulations.

A vaccine which protects only women would be expected to reduce HSV infection and disease in vaccinated women, decrease the rate of neonatal HSV infection, have an impact on the epidemic spread of genital herpes in men and women, and finally possibly reduce acquisition and transmission of HIV infection. Failure to protect HSV-1 seropositive women may result if vaccination does not add to the natural protection provided by HSV-1. In this case administration of vaccine to young children, before HSV1 occurs, would not be particularly helpful. Lack of efficacy of vaccines in HSV1-infected individuals would render the vaccine useless in developing countries, where HSV-1 infection is almost universal.

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Malaria

Disease burden. Malaria is by far the world's most important tropical parasitic disease, and kills more people than any other communicable disease except tuberculosis. Malaria is a public health problem today in more than 90 countries, inhabited by a total of some 2 400 million people - 40% of the world's population. Malaria is endemic in a total of 101 countries and territories: 45 countries in WHO's African Region, 21 in its Americas Region, 4 in its European region, 14 in its Eastern Mediterranean Region, 8 in its South-East Asia Region, and 9 in WHO's Western Pacific Region. Worldwide prevalence of the disease is in the order of 300-500 million clinical cases each year. More than 90% of all malaria cases are in sub-Saharan Africa.

Mortality due to malaria is estimated to be over 1.1 million deaths each year (WHO , 2002). The vast majority of deaths occur among young children in Africa, especially in remote rural areas with poor access to health services. Malaria kills one child every 30 seconds. This preventable disease has reached epidemic proportions in many regions of the world, and continues to spread unchecked. In absolute numbers, malaria kills 3 000 children under five years of age per day. It is a death toll that far exceeds the mortality rate from AIDS. African children under five years of age are chronic victims of malaria, suffering an average of six bouts a year. Fatally afflicted children often die less than 72 hours after developing symptoms. In those children who survive, malaria also drains vital nutrients, impairing their physical and intellectual development. Malarial sickness is also one of the principal reasons for poor school attendance. Other high-risk groups are women during pregnancy, and non-immune travelers, refugees, displaced persons and laborers entering endemic areas. During pregnancy, malaria causes severe anemia, and is a major factor contributing to maternal deaths in malaria endemic regions. Pregnant mothers who have malaria and are HIV-positive are more likely to transmit HIV to their newborn. In many developing countries and in Africa especially, malaria exacts an enormous toll in lives, in medical costs, and in days of labor lost. The causative agents in humans are four species of Plasmodium protozoa (single-celled parasites) - P.falciparum, P.vivax, P.ovale and P.malariae transmitted by Anopheline mosquitoes, the number and type P.falciparum, P.vivax, P.ovale and P.malariae transmitted by Anopheline mosquitoes, the number and type of which determine the extent of transmission in a given area. Transmission of malaria is affected by climate and geography, and often coincides with the rainy season. Of these, P.falciparum accounts for the majority of infections and is the most lethal. Malaria is a curable disease if promptly diagnosed and adequately treated.

The geographical area affected by malaria has shrunk considerably over the past 50 years, but control is becoming more difficult and gains are being eroded. Malaria's reach is spreading. In malaria endemic parts of the world, a change in risk of malaria can be the unintended result of economic activity or agricultural policy that changes the use of land (e.g. creation of dams, irrigation schemes, commercial tree cropping and deforestation). "Global warming" and other climatic events such as "El Niño" also play their role in increasing risk of disease. The disease has now spread to highland areas of Africa, for example, while El Niño events have an impact on malaria because the associated weather disturbances influence vector breeding sites, and hence transmission of the disease. Many areas have experienced dramatic increases in the incidence of malaria during extreme weather events correlated to El Niño. Moreover, outbreaks may not only be larger, but more severe, as populations affected may not have high levels of immunity. Quantitative leaps in malaria incidence coincident with ENSO (El Niño/Southern Oscillation) events have been recorded around the world: in Bolivia, Columbia, Ecuador, Peru and

Venezuela in South America, in Rwanda in Africa, and in Pakistan and Sri Lanka in Asia.

More than any other disease, malaria hits the poor. Malaria endemic countries are some of the world's poorest. Costs to countries include costs for control and lost workdays - estimated to be 1-5% of GPD in Africa. For the individual, costs include the price of treatment and prevention, and lost income. Rural communities are particularly affected. In rural areas, the rainy season is often a time of intense agricultural activity, when poor families earn most of their annual income. Malaria can make these families even poorer. In children, malaria leads to chronic school absenteeism and there can be impairment of learning ability. Urban malaria is increasing due to unplanned development around large cities, particularly in Africa and South Asia.

The estimated costs of malaria, in terms of strains on the health systems and economic activity lost, are enormous. In affected countries, as many as 3 in 10 hospital beds are occupied by victims of malaria. In Africa, where malaria reaches a peak at harvest time and hits young adults especially hard, a single bout of the disease costs an estimated equivalent of 10 working days. Research indicates that affected families clear only 40% of land for crops compared with healthy families. Knowledge about malaria is markedly low among affected populations. In one recent survey in Ghana, for example, half the respondents did not know that mosquitoes transmit malaria. The direct and indirect costs of malaria in sub-Saharan Africa exceed US$ 2 billion, according to 1997 estimates. According to UNICEF , the average cost for each nation in Africa to implement malaria control programmes is estimated to be at least US$ 300 000 a year. This amounts to about six US cents (US$ 0.06) per person for a country of 5 million people.

A limited number of drugs for treatment of malaria are available today. Due to worsening problems of drug resistance in many parts of the world, adequate treatment of malaria is becoming increasingly difficult. Although some new drugs have appeared in the last 20 years (e.g., mefloquine, halofantrine, artemisinin derivatives, malarone, atovaquone + proguanil, co-artemether), new (especially inexpensive and affordable) drugs and more practical formulations of existing drugs/compounds are badly needed.

Vaccines. International efforts to combat malaria are unprecedented (see WHO website) through a Global Malaria Control Strategy whose activities are coordinated by WHO's Programme on Communicable Diseases (CDS), Roll Back Malaria coordinating the efforts of four UN-System agencies (UNDP , UNICEF , WHO and the World Bank) launched on 30 October 1998, Multilateral Initiative on Malaria (MIM) launched in Dakar in January 1997 when a number of institutions (from both public and private sectors) joined forces to promote malaria research in Africa. The UNDP/World Bank/WHO Special Programme on Tropical Diseases (WHO/TDR) has joined the initiative, establishing a Task Force to address the needs of endemic countries and to fund activities related to strengthening research capacities in malaria. The Task Force has mobilized around 40 countries and 161 partners for submitting proposals for review. Fifteen partnership projects involving 20 African and 5 European countries and the USA have been funded. The main malaria vaccine funding agencies are the USA NIH , the European Union , either directly of through the European Malaria Vaccine Initiative (EMVI) , the USAID , the Malaria Vaccine Initiative (MVI) and Rockefeller Foundation . There are four general categories of malaria vaccine candidates, each representing a different stage of intervention. Virtually all the malaria vaccine candidates (with the exception of GPI anchor antigen described below) are cell surface antigens present during one of the three developmental stages of the Plasmodium parasite. Pre-erythrocytic (sporozoite) vaccines are those directed against the sporozoite and liver stages of the malaria parasite. The sporozoite is the form of the parasite introduced into the human host by the bite of an infected mosquito and that invades liver cells. A sporozoite vaccine could prevent infection either by blocking invasion of liver cells (antibody response) or destroying infected liver cells (cell-mediated response) by preventing release of parasites into the bloodstream. The asexual blood-stage (erythrocytic) vaccines are directed against the merozoite stage of the parasite, which invades and replicates in the red blood cells. A blood-stage vaccine would be expected to reduce both the severity and duration of the disease by decreasing the blood parasite density, which correlates with reduced disease symptoms and risk of death. The transmission-blocking vaccines are designed to raise antibodies (in humans) against the gamete stage of the parasite present in the mosquito gut. Such antibodies taken up by a mosquito during a blood meal should block further parasite development in the mosquito, becoming a non-infectious vector. Blocking transmission of the parasite could reduce infectivity of the mosquitoes (carrying fewer parasites) and extend the useful life of a pre-erythrocytic or blood-stage vaccine by preventing transmission of antibody-resistant mutants. A fourth type of potential malaria vaccine is an anti-disease vaccine. This approach to a vaccine involves the identification of parasite toxins that contribute to disease. The glycosylphosphatidyl inositol (GPI) anchor, which tethers several of the parasite antigens to the membrane, has been shown to be highly toxic in mouse models. GPI as a vaccine would have to be detoxified enough to be safe but the potential for disease attenuation with this approach is real. Most investigators now acknowledge that a combination vaccine (multi-antigen, multi-stage) will probably be the best approach to effective vaccination. The various malaria vaccine candidate antigens are expressed and manufactured in a number of different ways including recombinant protein, DNA vaccine constructs, viral-vectored constructs, synthetic peptides, and chimeric proteins. The Plasmodium genome is very A-T rich, unlike most of the microbial organisms (bacteria, yeast or virus) or animals used to express recombinant parasite antigens, and the organism has quite different codon usage. Enhanced expression of recombinant Plasmodium antigens may be obtained by creating synthetic genes using optimized codons according to the organism used for expression.

The most advanced and well-documented pre-erythrocytic (liver-stage) vaccine candidates are derived from the circumsporozoite (CS) antigen present on the sporozoite. Such a vaccine candidate developed by GlaxoSmithKline and the Walter Reed Army Institute of Research (WRAIR) , is referred to as RTS,S/ASO2. This vaccine is comprised of the antigenic C-terminus (amino acids 207-395) of the CS gene from P. falciparum fused to the hepatitis B surface antigen. This chimeric polypeptide containing the hepatitis B surface antigen is co-expressed with hepatitis B surface antigen in Saccaromyces cerevisiae. Initial Phase I clinical trials of RTS,S formulated with the ASO2 adjuvant (containing MPL, QS21 and an

oil-in-water emulsion) showed protection against sporozoite challenge in 6 out of 7 volunteers. More recently, a dose-range Phase I/II study showed levels of efficacy from 30% (single dose) to 55% (3 doses). Overall protective efficacy was 41% among 41 vaccinees. Further trials in a pediatric population in The Gambia are now in progress (www.malariavaccine.org). Current studies are aimed at combining RTS,S with the blood-stage antigen MSP1 (see below).

Another CS-based vaccine candidate includes a 102-amino acid synthetic peptide representing the antigenic C-terminus of the circumsporozoite antigen . The peptide was safe and immunogenic in humans (no challenge). This vaccine candidate will soon enter Phase I/II trials for safety and efficacy in Europe. In addition, Apovia (USA) is developing with MVI funding a vaccine based on CS determinants expressed on Hepatitis B core particles This vaccine should soon enter clinical development.

The Department of Defense (USA) in collaboration with Vical, Inc . is developing DNA vaccines for malaria (the Multi-Stage DNA Operation, MuStDO) that includes a liver-stage DNA vaccine candidate encoding the CS protein of P. falciparum. This DNA vaccine tested in Phase I showed no serious adverse events and no detectable DNA autoantibodies after a one-year follow-up but the vaccination failed to induce antigen-specific antibodies.

A multiple-antigen version of the DNA vaccine, MuStDO 5, encodes five different liver-stage antigens including CS and the additional antigens: liver stage antigens 1 and 3 (LSA 1 and 3), exported protein 1 (EXP1), all having shown to be protective in mouse models , and sporozoite surface protein 2 (SSP2, previously tested in animals as part of a DNA vaccine mix and also known as thrombospondin-related adhesive protein, TRAP). MuStDo 5 is manufactured as a combination of five separate plasmids. The DNA vaccine administered with GM-CSF DNA as adjuvant was safe and well tolerated in mice and rabbits. The LSA 3 protein has been demonstrated to induce protective immunity against P. falciparum infection in the chimpanzee model. Various formulations of this antigen (peptides, lipopeptides, and DNA vaccine) are currently targeted for clinical development.

Several groups are using a prime-boost approach by priming with a DNA vaccine and boosting with either recombinant antigen or viral vectors, shown to be more immunogenic than either vaccine alone.

Another vaccine development approach targeting the pre-erythrocytic parasite is focused on the intracellular liver stage parasite. Several known antigens expressed by sporozoites or merozoites can also be expressed by liver stage parasites. Various studies conducted in endemic areas have linked liver stage antigen 1(LSA-1) with protective immunity. B-cell and T-cell epitopes in LSA-1 and LSA-3 have been associated with protective immune responses in these studies.

Additional antigens that have been targeted for vaccine development because of identification of epitopes associated with protective immunity include the sporozoite and liver stage antigen (SALSA) ,sporozoite threonine and aspargine rich protein (STARP - also expressed in sporozoites) , and the glutamate-rich protein (GLURP) . The progress in the field of peptide synthesis now permits the synthesis of long chains of synthetic peptides (LSP) which allows for the inclusion of multiple protective epitopes. This long synthetic peptide approach to malaria vaccine design is being pursued by several collaborative groups in Europe and Africa.

Asexual blood-stage vaccine candidates. The most advanced asexual blood stage vaccine is merozoite surface protein 1 (MSP1). MSP1 forms part of a complex that is thought to be involved in red blood-cell invasion and antibodies to MSP1 have been shown to block parasite invasion of red blood cells in-vitro. MSP1 contains the presence of two connected cysteine-containing epidermal growth factor (EGF)-like modules required to maintain the conformation-dependent epitopes needed to generate protective antibodies . The EGF-like domains is conserved across all species of Plasmodium, thus this region is a prime focus of current MSP1 vaccine candidates. Several groups work on MSP1 either as the entire molecule, the 42kDa C-terminal moiety, the further-processed 19kDa fragment, or as part of a hybrid molecule. Baculovirus, E. coli, and yeast (Saccharomyces or Pichia) are the expression systems used for recombinant antigen production. Recombinant MSP1 (42kDa or 19kDa), produced in each of these different systems, has been shown to protect both mice and monkeys against lethal parasite challenge. Several DNA vaccine constructs are also being tested. Most of these vaccines are in pre-clinical stage of optimization prior GMP manufacturing for Phase I/II trials.

A number of additional merozoite surface protein (MSP) antigens are under development as vaccine candidates (MSP2, 3, 4, 5, 8 and 9) . These related molecules contain one or more of the hallmark EGF-like domains present in MSP1. MSP5 is of particular interest because it lacks the sequence variation between different isolates of P. falciparum from different geographical locations (typically seen with most of the merozoite surface proteins), which may simplify vaccine formulation.

Currently most advanced along the vaccine development pathway of blood-stage malaria vaccine candidates is the 'Combination B' vaccine candidate. This vaccine combines MSP-1 and MSP-2 with Plasmodium falciparum ring-infected erythrocyte(RESA). Recently, phase I/IIb trials of this vaccine in Papua New Guinea children aged 5-9 showed a 62 % reduction in parasite density in participants who were not pre-treated with sulfadoxine-pyrimethamine before vaccination . This trial highlighted the issue of clearing parasitemia before vaccination with treatment as the efficacy of the vaccine was only significant in the group who were not pre-treated. It also demonstrated possible vaccine-induced selective pressure on the MSP-2 component of the vaccine underlining the importance of development strategies that focus incorporating all significant genotype or highly conserved antigens in vaccine design.

Two other promising P. falciparum asexual blood-stage candidate antigens are the apical membrane antigen-1 (AMA-1) and erythrocyte binding antigen-175 (EBA-175) . There are currently 4-5 different laboratories developing these antigens as vaccine candidates expressed either in E. coli, Pichia pastoris

or as a DNA prime-boost vaccine.

Transmission-blocking vaccine candidates. The leading candidate vaccines contain the P. falciparum surface protein antigens Pfs 25 and Pfs 28 or the P. vivax homologues referred to as Pvs25 and 28. Currently, transmission-blocking antigens Pvs28, Pvs28, and Pfs25 are being developed at the NIH (USA) as recombinant yeast-secreted proteins (S. cerevisiae). Initial human Phase I safety, immunogenicity and in vitro efficacy trials have been done for Pfs25 and might be following soon for Pvs25. Other sexual stage-specific antigens that are being developed as transmission-blocking vaccines are Pfs48/45 and Pfs230.

Anti-toxic candidate vaccine - the anti-GPI vaccine Anti-disease vaccines are also being developed that involve direct immunization against parasite toxins that are identified as the cause of disease pathology. The identification of these toxins must be followed by characterization of the immune response to the toxin, focusing on it's subsequent neutralization by antibodies and most importantly, prevention of disease pathology, in order to be considered as a potential anti-disease malaria vaccine candidate.

The glycosylphosphatidylinositol (GPI) anchor, which tethers several of the parasite antigens to the membrane, has been shown to be highly toxic in mouse models, and is currently being developed as a carbohydrate anti-toxic vaccine. A study testing synthetic GPI in rodent models of malaria appeared to show that the candidate anti-toxic vaccine was immunogenic and protected the rodent model from significant malaria pathologies and mortalities . Following this initial proof-of-principle in an animal model, further development of the malaria toxin neutralization as a vaccine strategy continues.

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DOCUMENT II

DOCUMENT II

Portfolio of candidate malaria vaccines currently in development
February 2004

Please help IVR keep this document up-to-date and send any updates/comments/changes to Zarifah Reed (reedz@who.int)

Activities completed or ongoing are marked with a bold X
Support for activities indicated with colour and without an X have been secured
The various stages are considered as initiated at the steps indicated below:
Preclinical development stage: serious process development has been initiated
Phase 1a: first volunteer recruited for phase 1 in industrialized country
Phase 2a: first volunteer recruited for challenge study in industrialized country
Phase 1b: first volunteer recruited for phase 1 in disease endemic country
Phase 2b: first volunteer recruited for phase 2 in disease endemic country
Pivotal: first volunteer recruited for clinical study leading to licensure

Pre-erythrocytic vaccines

	Research	Preclinical development	Phase 1a	Phase 2a	Phase 1b	Phase 2b	Pivotal
CSP							
HBSAg-CSP chimeric mixed VLP (RTS,S)/AS02A (GSK)	**X**	**X**	**X**	**X**			
HBSAg-CSP chimeric mixed VLP (RTS,S)/AS02A and (RTS,S)/AS01B (WRAIR/GSK)							
HBCAg-CSP VLP (Malarivax Apovia)							
Modified Vaccinia Ankara (MVA) CSP tested in combination with RTS,S/AS02 (Oxford-GSK)	**X**						
Recombinant adenovirus CSP (NYU)							
Recombinant adenovirus CSP (WRAIR/Crucell Holland)							
Recombinant influenza CSP (NYU)							
Recombinant vaccinia CSP (NYU)							
Recombinant Sindbis virus CSP (NYU)							

	MVI		USAID		WHO/TDR
	European Commission		NIAID		EMVI
	Wellcome Trust		US Department of Defense		Support from institution or industry
			Funding by this agency is completed		

Pre-erythrocytic vaccines – CSP (continued)	Research	Preclinical development	Phase 1a	Phase 2a	Phase 1b	Phase 2b	Pivotal
Recombinant Yellow Fever virus CSP (NYU)	X						
Long synthetic CSP peptide (Lausanne)		X	X				
CSP DNA immunization (NMRC)	X	X	X				
Long Vivax CSP C-terminus 72 AA Synthetic peptide (MVDC)	X	X	X				
Long Vivax CSP N-terminus 77AA Synthetic peptide (MVDC)	X	X	X				
Long Vivax CSP repeat 48 AA Synthetic peptide (MVDC)	X	X	X				
Other antigens							
Long synthetic LSA-3 peptide (Pasteur Institute)	X						
L. lactis expressed recombinant LSA-3 protein + lipopeptides (Institut Pasteur)	X	X					
E. coli recombinant LSA-3 (WRAIR)							
E. coli recombinant LSA-1(LSA-NRC) (WRAIR)							
Adenovirus vectored LSA-1(LSA-NRC) (WRAIR/Crucell Holland)							
Modified Vaccinia Ankara (MVA) CSP + LSA-1 epitope (Oxford)							
Fowl Pox 9 CSP + LSA-1 epitope (Oxford)							
Fowl Pox 9 CSP + LSA-1 epitope/ Modified Vaccinia Ankara (MVA) CSP + LSA-1 epitope (Oxford)	X	X					
DNA MVA prime-boost Multi-epitope(ME) string + TRAP (Oxford)							
Fowl Pox 9 MVA prime-boost ME string + TRAP (Oxford)							

	MVI		USAID		WHO/TDR
	European Commission		NIAID		EMVI
	Wellcome Trust		US Department of Defense		Support from institution or industry
			Funding by this agency is completed		

Pre-erythrocytic vaccines – CSP (continued)		Preclinical development	Phase 1a	Phase 2a	Phase 1b	Phase 2b	Pivotal
Recombinant BCG-vectored vaccine CSP + 2 additional pre-erythrocytic antigens (Towson State University)							
Drosophila melanogaster recombinant LSA-1 Hawaii Biotech, Inc.)							
Multi- pre-erythrocytic epitope DNA vaccination (Epimmune/NMRC)	X						
Attenuated P. falciparum sporozoite vaccine (Sanaria)							

Blood Stage vaccines	Research	Preclinical development	Phase 1a	Phase 2a	Phase 1b	Phase 2b	Pivotal
MSP-1							
E. coli expressed MSP-1 19kD recombinant protein (ICGEB)		X					
E. coli expressed MSP-1 42kD recombinant protein (ICGEB)							
Recombinant full length MSP-1 3D7 (Heidelberg/WRAIR)	X	X					
Recombinant full length MSP-1 FCB1 (Heidelberg/WRAIR)	X	X					
Recombinant full length MSP-1 3D7 + FCB1 (Heidelberg/WRAIR)	X	X					
Baculovirus recombinant protein MSP-1 19kD (Pasteur Institute)							
Baculovirus recombinant protein MSP-1 42kD FUP (U of Hawaii/Antigenics)	X						
Transgenic mammals expressed MSP-1 42 FVO (GTC Biotherapeutics/SAIC)							
P Pastoris recombinant protein MSP-1 19kD mutant (Mill Hill)							
E. coli expressed recombinant protein MSP-1 42Kd 3D7 (FMP-1)(WRAIR)	X	X	X	X			
E. coli expressed recombinant protein MSP-1 42Kd FVO (FMP-9)(WRAIR)							

	MVI		USAID		WHO/TDR
	European Commission		NIAID		EMVI
	Wellcome Trust		US Department of Defense		Support from institution or industry
			Funding by this agency is completed		

Blood Stage vaccines – MSP-1 (continued)	Research	Preclinical development	Phase 1a	Phase 2a	Phase 1b	Phase 2b	Pivotal
P pastoris expressed recombinant protein MSP-1 42Kd 3D7 (MVDU)							
P pastoris expressed recombinant protein MSP-1 42Kd FVO (MVDU)							
P pastoris recombinant AMA-1 and MSP-1 chimera (SMMHS)							
E. coli recombinant MSP1-42-kDa-EBA-175 chimera (WRAIR)	X	X					
E. coli expressed recombinant MSP1-19 and EBA-175 F1 domain protein (ICGEB)							
D. melamogaster expressed MSP1 19 kD protein (Hawaii Biotech, Inc.)							
D. melamogaster expressed MSP1 42 kD protein (Hawaii Biotech, Inc.)							
BCG vectored MSP-1 (AECOM)							
Salmonella-vectored MSP-1 (U. Maryland)							
Other MSPs							
Long synthetic peptide MSP-2 (Lausanne)	X	X					
E. coli expressed recombinant protein MSP-2 3D7+ (FC27) (La Trobe)	X						
Long synthetic peptide MSP-3 (Pasteur Institute)	X	X	X		X		
E. coli expressed recombinant MSP-4 protein (Monash)	X						
E. coli expressed recombinant MSP-5 protein (Monash)							
MSP-3-GLURP hybrid vaccine (SSI)	X	X	X		X		
AMA-1							
E. coli recombinant protein AMA-1 (Australia)							
E. coli expressed recombinant protein AMA-1 3D7 (MVDU)							

	MVI		USAID		WHO/TDR
	European Commission		NIAID		EMVI
	Wellcome Trust		US Department of Defense		Support from institution or industry
			Funding by this agency is completed		

Blood Stage vaccines – AMA-1 (continued)	Research	Preclinical development	Phase 1a	Phase 2a	Phase 1b	Phase 2b	Pivotal
E. coli expressed recombinant protein AMA-1 FVO (MVDU)							
P pastoris expressed recombinant AMA-1 protein (BPRC)		X	X				
E. coli recombinant protein AMA-1 FVO (FMP10)(WRAIR)							
E. coli recombinant protein AMA-1 3D7 (FMP2.1)(WRAIR)							
EBA-175 and DBP							
E. coli expressed recombinant Region II Duffy Binding Protein protein (ICGEB)							
E. coli expressed recombinant EBA-175 F1 domain protein (ICGEB)		X			X		
P pastoris recombinant protein EBA-175 (F1 +F2) (EntreMed/SAIC)							
Other proteins							
Long synthetic GLURP peptide (SSI)	X	X	X		X		
MAEBL (Notre Dame University)							
P. Pastoris expressed erythrocyte binding proteins EBP2/BAEBL (Entremed)							
E. coli expressed recombinant RAP-2 protein (QIMR)	X						
E. coli, P. pastoris, baculovirus expressed PfEMP1, different domains (various EU groups)		X					
P. falciparum synthetic GPI toxin (WEHI/MIT)							

	MVI		USAID		WHO/TDR
	European Commission		NIAID		EMVI
	Wellcome Trust		US Department of Defense		Support from institution or industry
			Funding by this agency is completed		

Transmission blocking vaccines							
	Research	Preclinical development	Phase 1a	Phase 2a	Phase 1b	Phase 2b	Pivotal
Saccharomyces recombinant protein PvS25 (MVDU)							
P Pastoris recombinant protein PfS25 (MVDU)							
Recombinant protein PfS48 (MVDU)							
Recombinant protein PfS48 (Nijmegen)							
DNA immunization PfS25 (JHU)							
DNA immunization PvS25 (JHU)							
DNA immunization PvS28 (JHU)							
Recombinant Pfs230 (Loyola University)							

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	European Commission		NIAID		EMVI
	Wellcome Trust		US Department of Defense		Support from institution or industry
			Funding by this agency is completed		

Combination (Multistage) Vaccines							
	Research	Preclinical development	Phase 1a	Phase 2a	Phase 1b	Phase 2b	Pivotal
Multi-epitope recombinant protein CSP, MSP-1, MSP-2, LSA-1, AMA-1, RAP-1, EBA-175 (FALVAC CDC)	X						
MVA prime-boost Fowl Pox 9 LSA3/D260; STARP; EXP1, Pfs16, TRAP, LSA-1 (Oxford)							
DNA in co-block polymer +/- viral boost CSP, SSP2, LSA-1, AMA-1, MSP-1 (NMRC)							
MVA CSP, SSP2, LSA-1, AMA-1, MSP-1 (NMRC)							
Recombinant *Salmonella*-vectored vaccine CSP, SSP2, LSA-1, MSP-1, individually as well as in combination (U Maryland)							
Recombinant *Shigella*-vectored vaccine CSP, SSP2, LSA-1, MSP-1, individually as well as in combination (U Maryland)							
Multivalent antigen expression/vaccine for malaria (Lifesensors, Inc.)							
Recombinant Adenovirus CSP, SSP2, LSA-1, AMA-1, MSP-1 (NMRC/Genvec)	X	X					
Recombinant FMP-1 plus RTS,S , MSP-1 3D7 + CSP (WRAIR)							
Mimetopes delivered on Virosome CSP, MSP-1, AMA-1 (Pevion)	X	X					

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